APPENDIX 6

PRODUCT MONOGRAPH

Estrogen Replacement Therapy

Cenestin™

(synthetic conjugated estrogens, A) Tablets

0.625 mg, 0.9 mg

DURAmed

DURAMED PHARMACEUTICALS

Contents

INTRODUCTION

Vasomotor Symptoms of Menopause

Although menopause is a natural event, a significant percentage of menopausal women suffer bothersome symptoms that often disrupt their everyday routine. Vasomotor complaints, which include hot flashes and night sweats, are the most common menopausal symptoms, occurring in approximately 60% of women within 3 months after their last menstrual period.[1] Of these women, 85% have hot flashes for at least 1 year and 25% to 50% experience hot flashes for more than 5 years.[1] In addition to vasomotor symptoms, a considerable number of women experience insomnia and fatigue[1], which might be related to sleep interrupted by hot flashes and night sweats.

Vasomotor symptoms are the primary reason menopausal women seek medical help. Because vasomotor and other symptoms of menopause are related to declining estrogen levels, the principal treatment for these symptoms is Estrogen Replacement Therapy (ERT). Cenestin™ (synthetic conjugated estrogens, A) Tablets have been found to be safe and effective in the treatment of moderate-to-severe vasomotor symptoms. This product is unique in that it is the first synthetic conjugated estrogens product that is derived from a starting mixture of plant extracts (soybean and yam) and has a patented slow-release formulation. In contrast, Premarin® (conjugated equine estrogens tablets), the only complex mixture conjugated estrogens product on the market before the approval of Cenestin™, is manufactured from the urine of pregnant horses.

Perimenopause, Menopause, and Postmenopause

Menopause, which occurs in all women typically between the ages of 45 and 55, signals the end of a woman's natural reproductive ability. Menopause is a gradual process, usually occurring over 3 to 5 years. The events surrounding menopause can be divided into 3 time periods—perimenopause, menopause, and postmenopause.[2] Perimenopause is the time immediately before and after menopause. Many women experience noticeable physical changes and symptoms during the perimenopausal stage. Menopause is the time of the

final menstrual period, indicating the cessation of ovarian function. Postmenopause begins immediately after the final menstrual period. It overlaps at first with the end of the perimenopause, then extends to the end of life.

Approximately 40 million women in the United States currently are perimenopausal. Within the next 5 years, nearly 20 million baby-boomer women will enter menopause. Although for most women, age determines menopausal status, women at any age who have their ovaries removed for health reasons undergo surgical menopause, in which menopause is completed all at once. (Estrogens are secreted primarily by the ovarian follicles. With the removal of the ovaries, this estrogen production ceases.) In women who undergo a hysterectomy, in which the uterus is removed but the ovaries are left intact, menstrual bleeding stops but menopause is still completed gradually.

During the climacteric transition, women experience considerable changes in circulating hormone levels. These changes are initiated by the aging of the ovaries and production of fewer ovarian follicles (immature eggs stored in the ovaries). Because of the reduced quality and function of the aging follicles, ovulation may not occur every month. As a result, the negative feedback mechanisms controlling hormone levels begin to fail. Starting in a woman's late 40s, levels of follicle-stimulating hormone (FSH), which causes a follicle to mature, gradually rise, peaking a few years after menopause.[3] A longer menstrual cycle and menstrual irregularities are signs of increasing FSH levels. Levels of luteinizing hormone (LH), which triggers the release of a ripened follicle from the ovary, remain fairly stable during the early perimenopausal transition, then increase by 3- to 4-fold during the year before and for up to 3 years after menopause. Similarly, levels of estrogen typically remain within normal limits during the perimenopausal transition, starting to decline only a few months before menopause. Sustained elevated levels of FSH and LH after menopause are conclusive evidence that the ovaries are no longer functioning.

The decline of estrogen levels, a hallmark of menopause, can cause several different symptoms in addition to hot flashes and night sweats. Vaginal dryness, causing itching and painful sexual intercourse, is a common complaint. Menopausal women also report muscle or joint pain, tenseness, irritability, dizziness, palpitations, depression, forgetfulness, lack of energy, shortness of breath, headaches, burning during urination, vaginal discharge, and incontinence.[4] As menopause progresses and estrogen levels plummet,

women become at greater risk for certain diseases, including heart disease and osteoporosis.

Estrogen Replacement Therapy

Estrogen is the standard therapy for treating menopausal symptoms. Estrogens administered as replacement therapy are metabolized and converted by the body in the same way as are endogenous estrogens and thus have similar effects. As previously noted, ERT can significantly decrease the occurrence and severity of vasomotor symptoms. The effects of ERT are both dose and duration dependent. The Food and Drug Administration (FDA) requires that ERT drug products be studied for the optimum dose for all indications. Not all ERT drug products are indicated for treating all postmenopausal symptoms. Cenestin™ is currently indicated for the treatment of moderate-to-severe vasomotor symptoms (MSVS).

Estrogen drug products act by regulating the transcription of a limited number of genes. Estrogens diffuse through cell membranes, distribute themselves throughout the cell, and bind to and activate the nuclear estrogen receptor, a DNA-binding protein found in estrogen-responsive tissues. The activated estrogen receptor binds to specific DNA sequences, or hormone-response elements, that enhance the transcription of adjacent genes and in turn lead to the observed effects of estrogen. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bones of women.

In women without an intact uterus, estrogen replacement therapy alone is sufficient. In women with an intact uterus, ERT can overstimulate the endometrium of the uterus, which increases the risk of endometrial cancer. To decrease this risk, estrogen and a progesterone hormone are used in combination. Called Hormone Replacement Therapy (HRT), this combination regimen can be given in several ways: cyclic sequential (in which estrogen is given for 21 to 25 days followed by a progestin, usually medroxyprogesterone, for 10 days to allow sloughing of the uterine lining); continuous sequential (in which estrogen is given continuously, with progestin added during the last week or so of the cycle); continuous combined (in which estrogen and progestin are given together for the duration of the cycle); or cyclic combined (in which estrogen and progestin are combined in one pill, but the composition of the pill changes throughout the cycle).

With the approval of Cenestin™ (synthetic conjugated estrogens, A) Tablets, physicians and their patients seeking treatment for their vasomotor symptoms can choose a plant-based product that provides a therapeutic alternative to the conjugated equine estrogens product.

PRODUCT DESCRIPTION

Source

Cenestin™ (synthetic conjugated estrogens, A) Tablets are derived from a starting mixture of soybean and yam extracts. Cenestin™ is manufactured under rigid conditions of containment, environmental control, and testing, resulting in a dependable and consistent product.

Physical and Chemical Characteristics

Cenestin™ tablets are round, color-coded by strength, film-coated, and debossed with letters and numbers. Cenestin™ tablets contain a blend of nine synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate, and sodium 17β-estradiol sulfate. See *Package Insert* for chemical formulae, molecular weights, and structural formulae.

Cenestin™ tablets contain ethylcellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide, and triethyl citrate. The 0.625 mg tablets also contain FD&C Red No. 40 aluminum lake. The 0.9 mg tablets are white and contain no color additives.

Conjugated estrogens are water soluble. They generally are unreactive chemically, but are easily interconverted enzymatically in the body.

Tablet Formulation

The Cenestin™ tablet formulation is designed to release the synthetic conjugated estrogens, A, slowly over a period of several hours. The slow release of estrogens is due to the patented formulation. The tablet core contains a gum-like material and the tablet is coated with an acid-resistant film-coat. When swallowed, the tablet's film-coat helps retard tablet dissolution in the acidic stomach. As the tablet passes on down to the intestine, this film-coat erodes. The tablet core is then exposed to liquid, which causes the gum to swell. The estrogens inside this gum matrix are then slowly exposed to the liquid, solubilized, and pass through the gut lining.

Indications

Cenestin™ is indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause.

Stability

The stability or expiration dating for Cenestin™ tablets is 4 years for 0.625 mg tablets and 3 years for 0.9 mg tablets in commercial package configurations when stored at a controlled room temperature of approximately 25°C (77°F), as defined in the *U.S. Pharmacopeia* (USP).

Favorable conditions for Cenestin™ are controlled room temperature and no humidity. Light does not affect stability.

This stability is based on data generated for each of the 9 estrogens in Cenestin™. Similar stability results were obtained for all 9 components as demonstrated for the major estrone component in Figure 1.

Test Methods and Specifications

The tests performed on Cenestin™ tablets include potency, dissolution testing, and uniformity checks on estrogenic substances.

Dissolution testing of Cenestin™ is done using a USP Method I (basket) dissolution apparatus. The rate of release of both sodium estrone sulfate and sodium equilin sulfate is determined at 2, 5, and 8 hours. Data for 4 commercial batches of Cenestin™ are presented in Figures 2 (estrone) and 3 (equilin).

The uniformity of Cenestin™ tablets is assessed by determining the amount of sodium estrone sulfate, sodium equilin sulfate, and sodium 17α-dihydroequilin sulfate in individual tablets and expressing the sum of

FIGURE 1

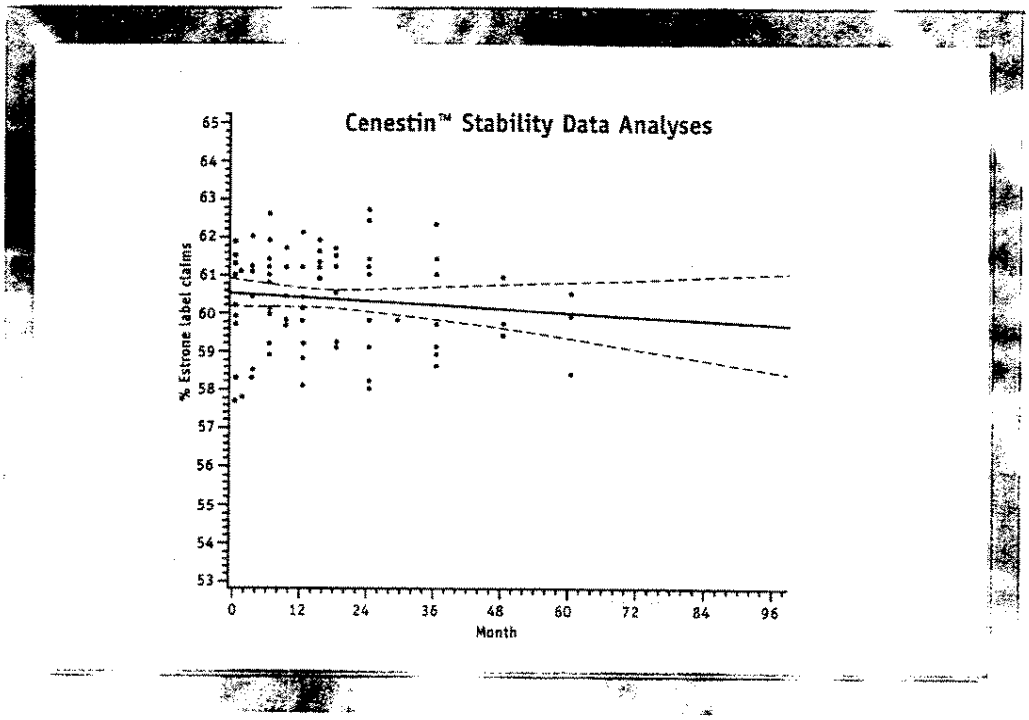
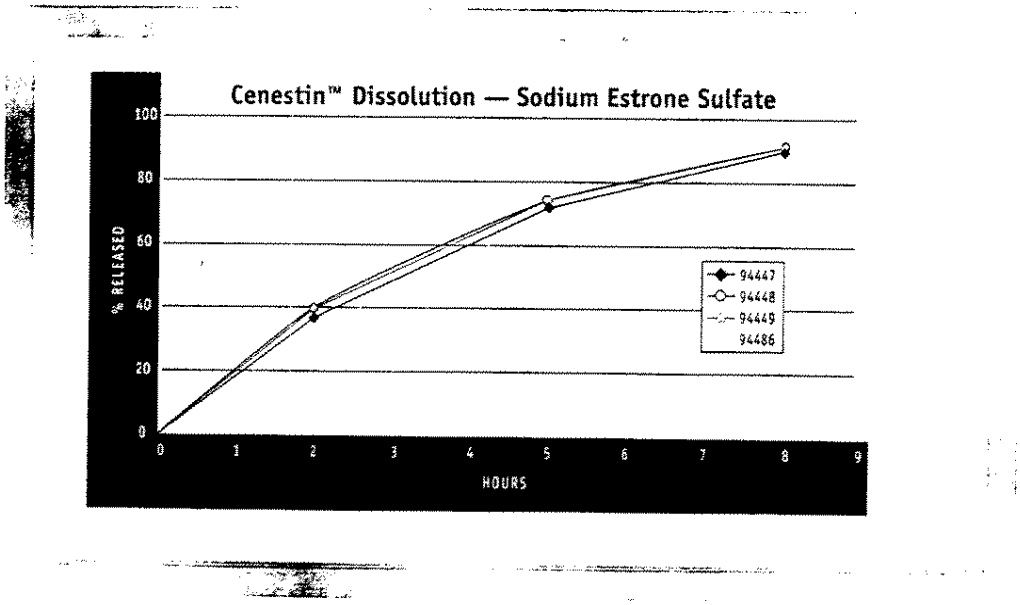
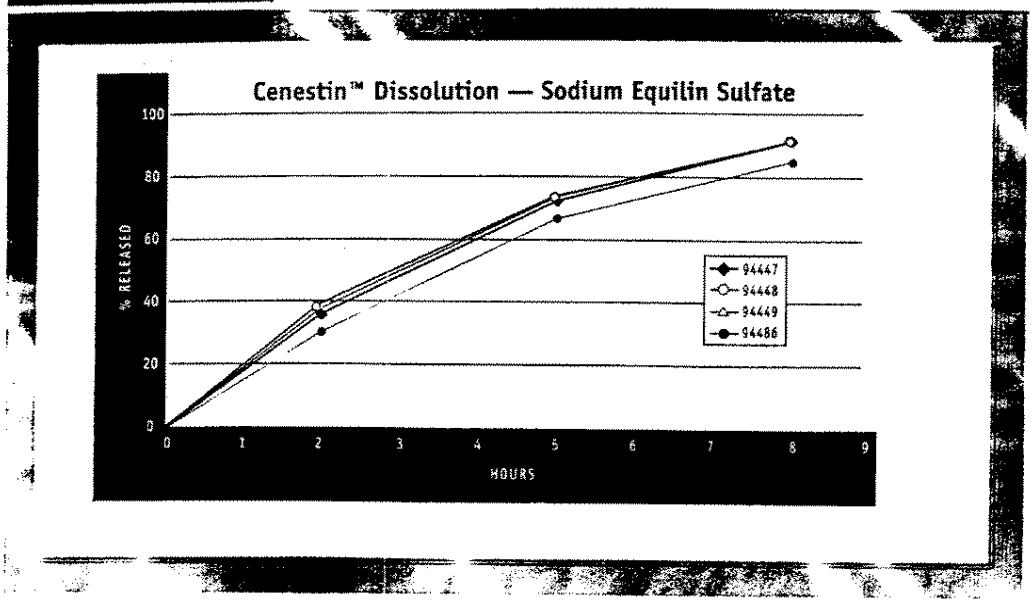


FIGURE 2





these 3 conjugated estrogens as a percent of the labeled content. Typical results of this assay and the ranges specified in USP 23 (1995) are listed in Table 1. The specifications apply to "Conjugated Estrogens USP," which referred to equine conjugated estrogens. A new monograph is to be developed for "synthetic conjugated estrogens," but is not yet available. Cenestin™ continues to be manufactured to meet these specifications. The results of this testing for the 4 validation batches are presented in Table 2. This data illustrates the consistency of the Cenestin™ 0.625 mg tablet produced by the unique patented manufacturing process of Duramed.

TABLE 1
Assay of Major Estrogen Components in Cenestin™

Estrogen Component Tested	USP 23 Specification (range)	Typical Test Results Cenestin 0.625 mg tab
Sodium Estrone Sulfate	52.5% to 61.5%	57%
Sodium Equilin Sulfate	22.5% to 30.5%	28%
Sodium 17α-dihydro-equilin Sulfate	13.5% to 19.5%	15%
Label claim (sum of 3 Estrogens)	(at midrange yield 100%)	100%

TABLE 2			
Batch ID	**Number of Tablets**	**Range**	**RSD%**
94447	30	84.9 – 120.1	5.3
94448	30	95.2 – 103.3	1.9
94449	30	94.7 – 110.0	3.3
94486	30	93.5 – 105.2	2.3

PHARMACOKINETICS AND PHARMACODYNAMICS

Absorption

Conjugated estrogens, whether derived from plant or animal sources, are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. The Cenestin™ tablet formulation is designed to release the synthetic conjugated estrogens, A, slowly over a period of several hours. Maximum plasma concentrations of conjugated and unconjugated estrogens are attained within 4 to 16 hours after oral administration. The absorption of Cenestin™ has been determined in an open label, randomized, 2-treatment (each consisting of 2 x 0.625 mg), 4-period, single dose, fully replicated, crossover study in 36 healthy, nonsmoking postmenopausal women between the ages of 21 and 65 weighing ±15% of ideal weights. Pharmacokinetic data for unconjugated and conjugated estrogens following a dose of 2 x 0.625 mg Cenestin™ is presented in Tables 3 and 4.

Figures 4 and 5 graphically present the mean bioavailability data for Cenestin™ 0.625 mg tablets following oral administration after an overnight fast. Figure 4 measures total estrone and equilin, and Figure 5 represents the free estrone and equilin.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex-hormone target organs. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone-

Pharmacokinetic Parameters for Unconjugated and Conjugated Estrogens in Healthy Postmenopausal Women under Fasting Conditions

TABLE 3
Pharmacokinetic Parameters of Unconjugated Estrogens Following a Dose of 2 x 0.625 mg Cenestin™

Drug	C_{max} (pg/mL) CV%	t_{max} (h) CV%	AUC_{0-72h} (pg·hr/mL) CV%
Baseline-corrected estrone	84.5 (41.7)	8.25 (35.6)	1749 (43.8)
Equilin	45.6 (47.3)	7.78 (28.8)	723 (67.9)

TABLE 4
Pharmacokinetic Parameters of Conjugated Estrogens Following a Dose of 2 x 0.625 mg Cenestin™

Drug	C_{max} (ng/mL) CV%	t_{max} (h) CV%	$t_{1/2}$ (h) CV%	AUC_{0-72h} (ng·hr/mL) CV%
Baseline-corrected estrone	4.43 (40.4)	7.7 (30.3)	10.6 (25.4)	69.89 (39.2)
Equilin	3.27 (43.5)	5.8 (31.1)	9.7 (23.0)	46.46 (47.5)

binding globulin (SHBG), and to a lesser degree to albumin. Conjugated estrogens bind mainly to albumin while the unconjugated estrogens bind to both albumin and SHBG.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Pharmacokinetic Profiles of Cenestin™ Tablets

FIGURE 4

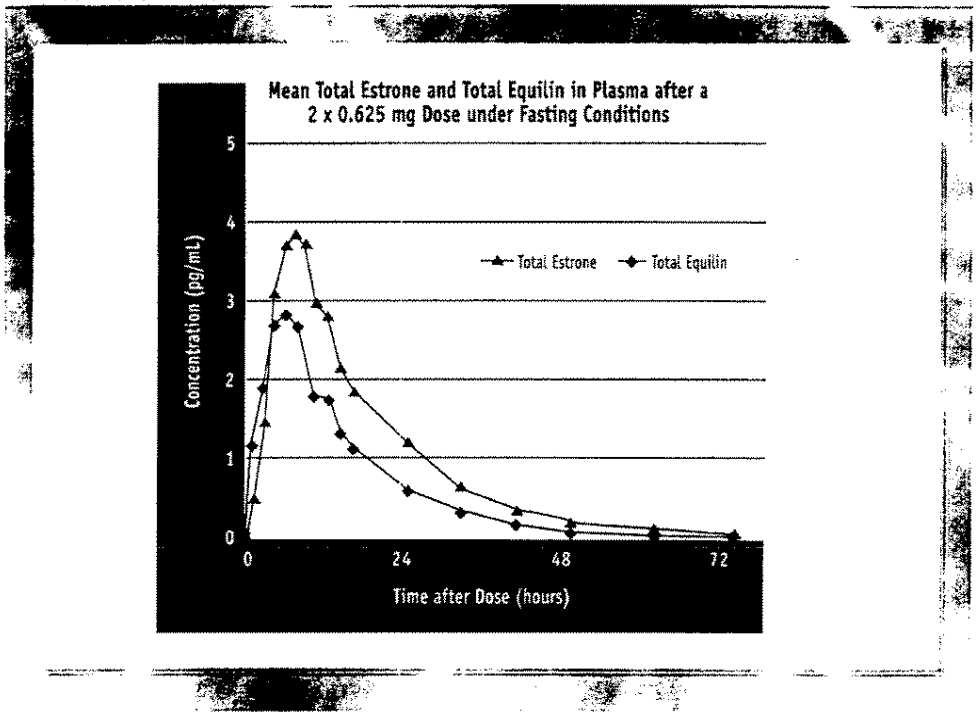
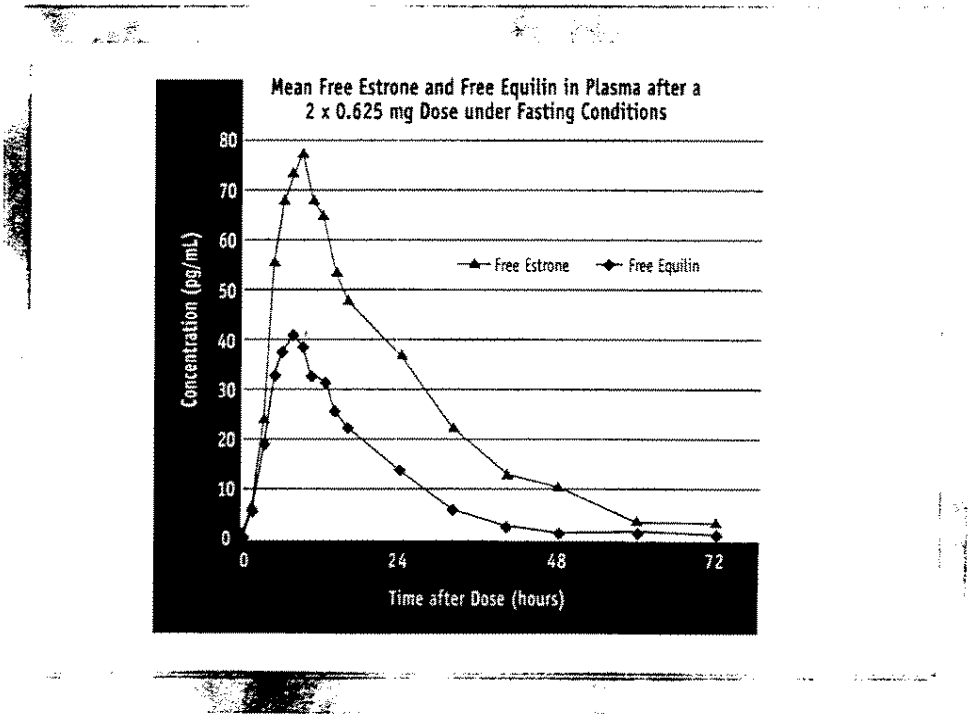


FIGURE 5



Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The apparent terminal elimination half-life ($t_{1/2}$) of conjugated estrone ranges from 4 to 18.5 hours and conjugated equilin from 4 to 17 hours.

CLINICAL STUDIES

Study Design

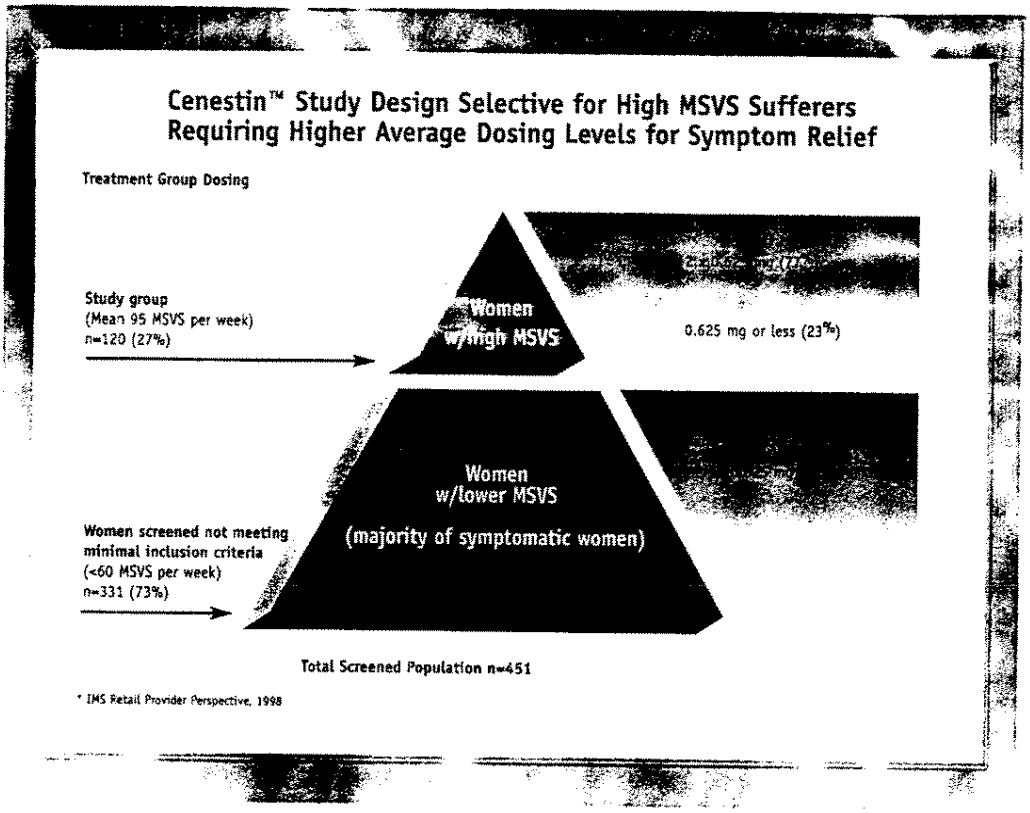
A randomized, double-blind, multicenter, placebo-controlled dose titration trial was conducted in the United States to evaluate the safety and effectiveness of Cenestin™ in treating vasomotor symptoms of menopause.[5] Women were eligible for the trial if they had experienced at least 60 MSVS (hot flashes and night sweats) per week for 2 consecutive weeks.

A total of 120 women aged 38 to 66 years (mean age, 48 years) were enrolled in the trial and randomly assigned to treatment with Cenestin™ tablets (n = 72) or placebo (n = 48) for 12 weeks. Patients in the Cenestin™ group were started on a single daily dose of 0.625 mg. After the first week of treatment, investigators could increase this dosage to 2 x 0.625 mg taken daily (maximum daily dose, 1.25 mg) in patients whose symptoms were not well controlled. The dosage could be decreased to 0.3 mg daily in patients who could not tolerate higher doses.

Only 27% of all symptomatic women screened for study met the strict inclusion criteria of >60 MSVS per week. In spite of severity of MSVS, 23% of women in the study were successfully treated with 0.625 mg or less. As expected from the study design, the majority of women (77%) had dosage increased to 2 x 0.625 mg. The design followed FDS guidelines. Outside clinical trials, physicians treat women with varying degrees of MSVS. The study population is graphically represented in Figure 6.

Each patient was asked to complete a daily diary in which she recorded the number and severity of hot flashes. Patients received brief training on the

FIGURE 6



use of the diaries and were interviewed frequently to monitor the quality of their diary entries.

The primary efficacy variable was the change in the number of MSVS at weeks 4, 8, and 12 in the intent-to-treat population. Analysis of variance was used to evaluate changes from baseline in the absolute number of vasomotor symptoms at each time point.

Study Features

The Cenestin™ clinical trial was designed to closely reflect the population diversity found in actual clinical practice. Consequently, minimal restrictions were placed on the type of patient who could be enrolled.

Most published studies of assessing the effectiveness of ERT for vasomotor symptoms include only those patients who had their last menstrual period 6 months (in some studies, 12 months) before dosing. In the Cenestin™ trial, patients could be enrolled even if they were still menstruating. These

perimenopausal women may suffer hot flashes, yet still have occasional (or even regular) periods. Many studies also require that a woman's FSH, or estrogen levels, meets certain criteria. The Cenestin™ clinical trial had no such requirement. The principal inclusion criterion was that on entry into the study, patients were having at least 60 moderate-to-severe hot flashes or night sweats per week.

Most studies assessing the effectiveness of ERT for vasomotor symptoms require that patients weigh within ±15% of normal weight for a given height, as listed in standard weight tables. In the Cenestin™ clinical trial, there was no upper limit on how much a woman could weigh.

Postmenopausal women often experience symptoms in addition to hot flashes that may require drug treatment. The Cenestin™ clinical trial restricted only those concomitant medications that could be expected to produce an estrogen-related response. Patients were allowed to take any other medication, provided that the regimen remained unchanged throughout the study period.

Most published studies of the effects of ERT or HRT for treating any indication are reported for white women only. However, in the Cenestin™ clinical trial, black women and those of other races were encouraged to enroll. The percentage of black women enrolled in the clinical trial was 28%, and the enrollment percentage of women of other races was 4%.

The dosing regimen used in the Cenestin™ clinical trial was designed to reflect current clinical practice. Before 1970, clinicians typically prescribed a continuous daily dose of estrogen. When the direct relationship between estrogen and endometrial cancer was established in the 1970s, physicians began to administer estrogen cyclically (three weeks on and one week off) in the belief that this schedule would cause sloughing of the endometrial lining of the uterus and thereby decrease the risk of endometrial cancer. In the 1980s, coadministration of a progestin became a means of decreasing the risk of endometrial cancer. During this time, researchers also determined that continuous daily administration of estrogen (in women without an intact uterus) or a combination of estrogen and progestin (in women with an intact uterus) offered the best risk-benefit ratio.

In the Cenestin™ clinical trial, all women received a continuous daily dose

of synthetic conjugated estrogens, A. In addition, the dose was titrated to effect, with patients receiving the lowest dose that controlled symptoms. Thus, all patients were randomized to 1 x 0.625 mg and anytime after 1 week of treatment could remain at that dose, increase to 2 x 0.625 mg (total 1.25 mg), or reduce the dose to 0.3 mg. Most clinical trials of estrogen products use a fixed dose.

Clinical Trial Results

Efficacy

A statistically significant decrease in the number of MSVS was seen in the Cenestin™ group compared with the placebo group (Table 5). This difference was apparent by week 4 and maintained throughout the 12-week study period. At baseline, patients in the Cenestin™ treatment group were experiencing a mean of 96.8 hot flashes per week. By week 12, the mean number of hot flashes in this group was 16.5 per week, a decrease of 80.3%. In the placebo treatment group, the mean number of hot flashes per week was 94.1 at baseline and 37.8 at week 12, a 56.3% decrease.

TABLE 5
Absolute Change and Percent Reduction in the Number of Moderate-to-Severe Vasomotor Symptoms (MSVS) in the Intent-to-Treat Population*

MSVS	Cenestin™ (n =70)	Placebo (n = 47)	Difference	*P* Value
Baseline				
Mean number	96.8 (42.6)	94.1 (33.9)	-	-
Week 4				
Mean number	28.7 (28.8)	45.7 (36.8)	-	-
Mean percent change	-68.1 (43.9)	-48.4 (46.2)	-19.9	0.0224
Week 8				
Mean number	18.6 (25.0)	39.8 (39.1)	-	-
Mean percent change	-78.3 (49.0)	-54.3 (49.2)	-24.6	0.0101
Week 12				
Mean number	16.5 (25.7)	37.8 (38.7)	-	-
Mean percent change	-80.3 (50.3)	-56.3 (48.0)	-24.7	0.0102

Data in parentheses are the standard deviation.
*Intent-to-treat population = 117.

In a separate, post hoc analysis of the data, the effect of race and weight on treatment response was examined. Of the 120 women enrolled, 68% were white, 28% were black, and 4% were of other races. As shown in Figure 7, there was no significant difference for relief of vasomotor symptoms in both white and black women in the Cenestin™ treatment group. Body mass index (BMI) also had no significant effect on response to treatment (Figure 8). Women in the study weighed from 109 to 271 pounds (mean weight, 165 pounds), and no difference was seen between those of normal weight and those who were overweight or obese.

FIGURE 7

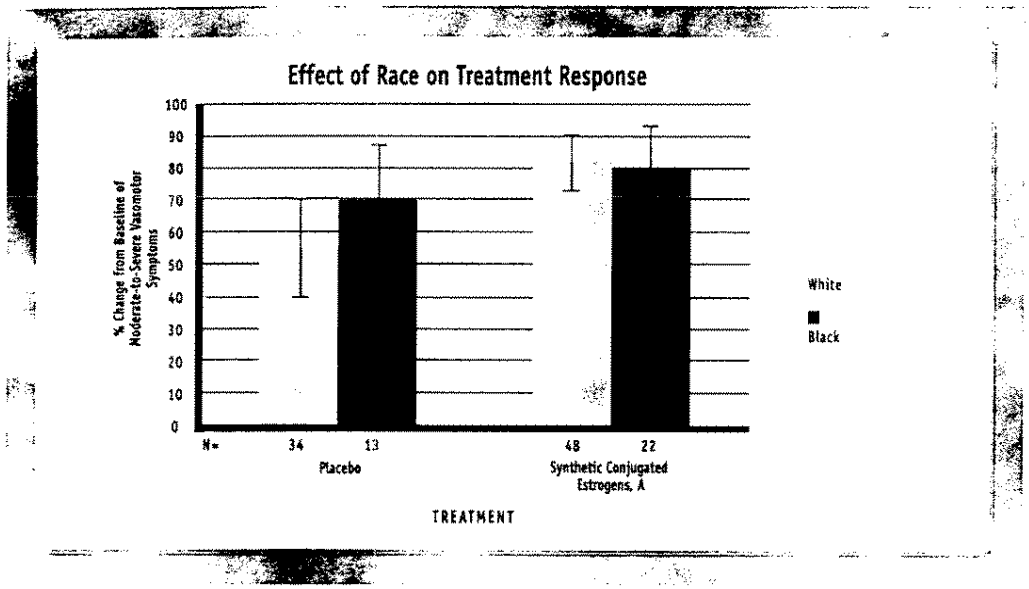
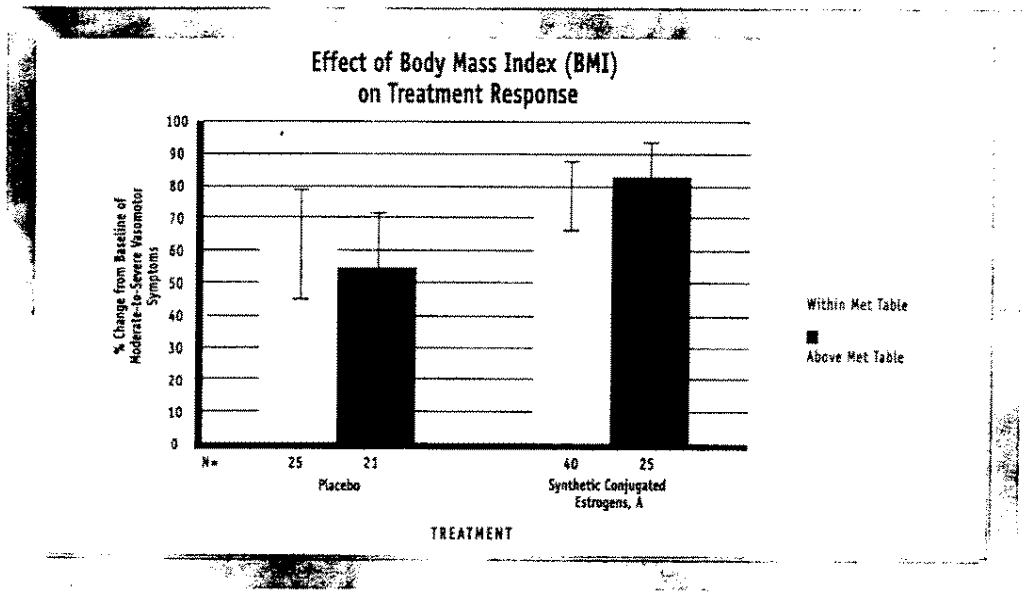


FIGURE 8



Effects on Lipids

In the pivotal clinical trial of Cenestin™, HDL and LDL were measured at baseline and after 12 weeks of treatment. The group receiving Cenestin™ experienced a statistically significant decrease in LDL (p=.0001) and an increase in HDL (p=.0001),[6] demonstrating that Cenestin™ has favorable lipid effects similar to other ERT drug products.

Safety

Cenestin™ is a safe product, as demonstrated in the clinical trial of 120 menopausal women. No serious adverse effects or deaths were reported in this study. The adverse effects that did occur in the Cenestin™ group were similar to those reported with other estrogen drug products.

Of the 120 patients who were enrolled in the Cenestin™ clinical trial, 109 completed all 12 weeks of the study. The 11 patients who did not complete the study (5 in the Cenestin™ group and 6 in the placebo group) withdrew or were withdrawn from the trial because of personal reasons, lack of compliance, or nonserious adverse events.

Among the 72 patients in the Cenestin™ group, 68 (94%) reported at least 1 adverse event. In the placebo group, 43 of the 48 patients (90%) reported at least 1 adverse event. The most common adverse effects in both groups (reported by more than 30% of patients) were headache, insomnia, asthenia, nervousness, paresthesia, depression, and myalgia (Table 6). There were no clinically significant changes or abnormalities in laboratory parameters or vital signs in either treatment group.

There was a slightly higher incidence of urogenital system adverse effects, breast pain, and metrorrhagia in the Cenestin™ group compared with the placebo group. Thirty patients (42%) in the Cenestin™ group versus 11 (23%) of those in the placebo group reported urogenital adverse events. Breast pain was reported by 21 patients (29%) treated with Cenestin™ and 7 patients (15%) given placebo. Metrorrhagia occurred in 10 patients (14%) in the Cenestin™ group and 3 patients (6%) in the placebo group. Of those women reporting metrorrhagia, 4 in the Cenestin™ group and 3 in the placebo group were still menstruating. Each of these adverse events is typical of those seen with estrogen drug products.

TABLE 6
Most Commonly Reported Adverse Events* in the Cenestin™ Clinical Trial
Percent of All Patients

Adverse Event	Cenestin™ (n = 72)	Placebo (n = 43)	Total (n = 120)
Headache	68	67	68
Insomnia	42	48	44
Asthenia	33	42	37
Nervousness	28	42	33
Paresthesia	33	31	33
Depression	28	38	32
Myalgia	28	31	29

* Reported by more than 30% of patients.

Contraindications, Precautions, and Warnings

Contraindications

Cenestin™, like all estrogen drug products, is contraindicated in persons who are or may be pregnant, have undiagnosed abnormal genital bleeding, have or may have breast cancer (except for appropriately selected patients being treated for metastatic disease), have or may have an estrogen-dependent neoplasia, or have active thrombophlebitis or thromboembolic disorders.

Precautions

The precautions that apply to Cenestin™ are similar to those for all estrogen drug products.

Addition of a progestin. In women with an intact uterus, the addition of a progestin to the estrogen therapy is recommended to decrease the risk of endometrial cancer. However, progestin itself is not without risks. When used as part of HRT, progestin can adversely affect lipoprotein levels (i.e., decreasing high-density lipoprotein [HDL] levels and increasing low-density lipoprotein [LDL] levels), impair glucose tolerance, and possibly enhance mitotic activity in breast epithelial tissue, although few epidemiologic data are available to address this point.

Elevated blood pressure. Substantial increases in blood pressure during ERT have been reported in a small number of cases, but these increases were attributed to idiosyncratic reactions to estrogens. In a randomized, placebo-controlled trial, estrogen had no generalized effect on blood pressure.

Familial hyperlipoproteinemia. Estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

Impaired liver function. Estrogens may be poorly metabolized in patients with impaired liver function.

Laboratory tests. Use of laboratory monitoring to determine dosing is not recommended. Estrogen administration should be guided by the patient's clinical response, and patients should receive the lowest dose that effectively controls their symptoms.

Drug and laboratory test interactions. Use of ERT can affect laboratory test results. These effects include accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and β-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; and increased plasminogen antigen and activity.

Women taking ERT may have increased levels of thyroid-binding globulin, leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine, T_4 levels as measured by column or by radioimmunoassay, or T_3 levels as measured by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated levels of thyroid-binding globulin. Free T_4 and free T_3 concentrations are unaltered.

Other binding proteins, such as corticosteroid-binding globulin and SHBG, may be elevated in serum, leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins (i.e., angiotensinogen/renin substrate, alpha-1-antitrypsin, and ceruloplasmin) may be increased.

Additional effects of ERT include increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels, impaired glucose tolerance, decreased response to the metyrapone test, and decreased serum folate concentrations.

Carcinogenesis, mutagenesis, and impairment of fertility. Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of cancers of the breast, uterus, cervix, vagina, testis, and liver.

Pregnancy. Estrogens are not indicated for use during pregnancy or the immediate postpartum period. Estrogens are not effective for preventing or treating threatened or habitual abortion. Treatment with diethylstilbestrol (DES) during pregnancy is associated with an increased risk of congenital defects and cancer in the reproductive organs of the fetus and possibly other birth defects. The use of DES during pregnancy has also been associated with a subsequent increased risk of breast cancer in the mothers.

Nursing mothers. As a general principle, nursing mothers should not take any drug unless clearly necessary because many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for preventing postpartum breast engorgement.

Pediatric use. Safety and efficacy of Cenestin™ for the treatment of vasomotor symptoms due to hypoestrogenism in pediatric patients have not been established.

Overdose

No serious ill effects have been reported in children who accidentally ingested large doses of an estrogen-containing product. An overdose of estrogen can cause nausea and vomiting and withdrawal bleeding in females.

Warnings for Estrogen Drug Products

The warnings that apply to estrogen drug products also apply to Cenestin™. These warnings have been developed over the years based on the considerable amount of data collected primarily from estrogen drug products no longer available. In 1998, the FDA recognized that changes were needed to reflect the current state of ERT, and proposed revision to the labeling required for all estrogen class products.[7] The black box warning now addresses only the risk of endometrial cancer for estrogens used unopposed (i.e., without a

concomitant progestin). The previous warning regarding use in pregnancy was incorporated into the *Precautions* section.

Endometrial cancer. The principal warning (highlighted by a black box in the prescribing information) alerts physicians to the increased risk of endometrial cancer in women with an intact uterus who are prescribed unopposed estrogen. The risk is approximately 2- to 12-fold greater in estrogen users compared with nonusers, depending on the duration of treatment and estrogen dose. Most studies show no significantly increased risk of endometrial cancer when estrogen is used for less than 1 year. However, women who use unopposed estrogen for 5 to 10 years or longer, are 15 to 24 times more likely than nonusers to develop endometrial cancer. This increased risk persists for at least 8 to 15 years after estrogen therapy is stopped.

Breast cancer. Although most studies have shown no increased risk of breast cancer in women who have used ERT, data are conflicting on whether there is an increased risk in women using estrogens for prolonged periods of time, especially for more than 10 years.

Venous thromboembolism. Three epidemiologic studies have found an increased risk of venous thromboembolism in users of ERT who did not have predisposing conditions for venous thromboembolism, such as a past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The findings were similar for ERT alone or with an added progestin and pertain to commonly used ERT types and doses, including 0.625 mg or more per day orally of conjugated estrogens, 1 mg or more per day orally of estradiol, and 50 µg or more per day of transdermal estradiol. The studies found that the risk of venous thromboembolism is about 1 case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2 to 3 cases per 10,000 women per year.

Cardiovascular disease. Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

Hypercalcemia. Administration of estrogens can lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, estrogen therapy should be stopped and appropriate measures taken to decrease the serum calcium level.

Gallbladder disease. A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery has been reported in postmenopausal women taking estrogen therapy.

DOSING CONSIDERATIONS

Dosage Ranges

For treatment of moderate-to-severe vasomotor symptoms associated with menopause, the lowest dose and regimen that will control symptoms should be chosen. Initial doses of 0.625 mg are recommended with titration up to 1.25 mg.

Dosage Strengths

Cenestin™ (synthetic conjugated estrogens, A) Tablets

- 0.625 mg tablets are available in containers of 30 (NDC 51285-442-30), 100 (NDC 51285-442-02), and 1000 (NDC 51285-442-05). Tablets are round, red, film-coated, and debossed with letters, ϕ, and number, 42.
- 0.9 mg tablets are available in containers of 30 (NDC 51285-443-30), 100 (NDC 51285-443-02), and 1000 (NDC 51285-443-05). Tablets are round, white, film-coated, and debossed with letters, ϕ, and number, 43.

Comparison with Other ERT Products

Comparison of ERT Products

Cenestin™ offers the first plant-derived conjugated estrogens alternative to Premarin®,[8] with a mixture of 9 estrogens and a slow-release formulation (Table 7). Note that none of the other plant-derived oral estrogen products are slow release and none of the slow-release transdermal products contain conjugated estrogens.

Table 7
Comparison of ERT Products

ERT Product	Source	*In Vivo* Release	Components	Definition
Premarin®	horse urine	slow	conjugated equine estrogens, androgens, progestins, and other undefined components	undefined
CENESTIN™	soy, yam	slow	synthetic conjugated estrogens, A	defined
Estratab®	soy, yam, others	rapid	estrone sulfate, equilin sulfate, "esterified estrogens"	defined
Menest®	soy, yam	rapid	estrone sulfate, equilin sulfate, "esterified estrogens"	defined
Ogen®	yam	rapid	estrone sulfate	defined
Ortho-Est®	yam	rapid	estrone sulfate	defined
Estrace®	soy, yam	rapid	estradiol	defined
Alora®	yam	slow	estradiol, transdermal patch	defined
Climera®	yam	slow	estradiol, transdermal patch	defined
Estraderm®	yam	slow	estradiol, transdermal patch	defined
FemPatch®	yam	slow	estradiol, transdermal patch	defined
Vivelle™	yam	slow	estradiol, transdermal patch	defined

Comparison with Premarin®

Composition

Cenestin™ contains 9 plant-derived estrogens versus Premarin®'s uncharacterized 28-plus estrogens, progestins, and androgens derived from pregnant mares' urine.

Cenestin
(synthetic conjugated estrogens, A)
0.625 mg, 0.9 mg

Unlike all other ERT oral preparations indicated for the treatment of vasomotor symptoms, both Cenestin™ and Premarin® are slow-release formulations, designed to provide a slow release of estrogens into the bloodstream. However, when you examine the source of the estrogens and their product formulations, significant differences can be seen.

Cenestin™ is a well-characterized product, formulated to contain nine estrogens in precisely controlled amounts. This composition is possible because the estrogens are synthesized from plant starting materials. In contrast, Premarin® is extracted from the urine of pregnant mares and must go through a blending process to achieve consistency within labeled specifications. The composition of Premarin® is still uncharacterized. While containing the same estrogens as Cenestin™, Premarin® also contains other steroids in addition to progestins and androgens.

Premarin® has at least 28 known steroidal components. Under requests for complete disclosure from the FDA's Center for Drug Evaluation and Research [CDER], Wyeth-Ayerst (W-A) describes their product as "a complex multi-component extract of pregnant mares' urine to which solka-floc (purified cellulose) is added to form a drug powder ... we call the material PCUD (preserved condensed urine desiccated)." Because of the "extraordinary complexity of this raw material" and the need to define the active ingredients in approved products, W-A continues to examine the content of Premarin® at the FDA's ongoing request for product definition.[9] By weight, estrogens are but a fraction of the steroids in this mix. In a letter to CDER (April, 1997), W-A officials admitted, "So far, we have identified approximately 0.9 mg of steroids per 0.625 mg Premarin® tablet ... we believe that approximately 1.3 mg of total steroids will ultimately be confirmed to be in each 0.625 mg tablet."[9]

A comparison of the ingredients in both products tells a dramatic story. Premarin® has more than the ten estrogenic substances stated on its label. The content and actions of these other substances have not been defined (Table 8).

Comparative Dissolution

Cenestin™ and Premarin® differ significantly in their formulation — a difference that impacts the *in vitro* dissolution profiles each will maintain with regular use.

TABLE 8
Summary of Product Content: Cenestin™ and Premarin®

Cenestin™ (synthetic conjugated estrogens, A) Slow-release formulation (soy and yam)	Premarin® (conjugated equine estrogens) Slow-release formulation (pregnant mares' urine)
Synthetic estrogenic substances Sodium estrone sulfate Sodium equilin sulfate Sodium 17α-dihydroequilin sulfate Sodium 17α-estradiol sulfate Sodium 17ß-dihydroequilin sulfate Sodium 17α-dihydroequilenin sulfate Sodium 17ß-dihydroequilenin sulfate Sodium equilenin sulfate Sodium 17ß-estradiol sulfate	**Estrogenic substances** Sodium estrone sulfate Sodium equilin sulfate Sodium 17α-dihydroequilin sulfate Sodium 17α-estradiol sulfate Sodium 17ß-dihydroequilin sulfate Sodium 17α-dihydroequilenin sulfate Sodium 17ß-dihydroequilenin sulfate Sodium equilenin sulfate Sodium 17ß-estradiol sulfate Sodium Δ8,9-dehydroestrone sulfate **Other Substances** 5,7,9 (10) Estratrien-3ß, 17-ß-diol 17α-Dihydro-Δ8,9-dehydroestrone 17ß-Dihydro-Δ8,9-dehydroestrone 5,7,9 (10) Estratrien-3ß-ol-17-one 2-Hydroxy-estrone 2-Methoxy-estrone **Progestins** 5α-Pregnane-3ß, 20ß-diol* 5α-Pregnane-3ß, 16α, 20ß-triol 5α-Preg-16-ene-3ß-ol-20-one 5α-Pregnane-3ß-ol-20-one Sodium 4 pregen-20-ol-3-one-20 sulfate 3ß-hydroxy-5(10), 7 estradiene 17-one-3-sulfate **Androgens** 5α-Androstan-3ß,17α-diol 5α-Androstan-3ß,16ß-diol 5α-Androstan-3ß,16α-diol 5α-Androstan-3ß-ol,16-one

* NOTE: W-A sources indicate 3 conjugated isomers present: 5α-Pregnane-3ß,20ß-diol-3 sulfate; 5α-Pregnane-3ß,20ß-diol-20 sulfate; 5α-Pregnane-3ß,20ß-diol-3,20 disulfate.[3]

Cenestin
(synthetic conjugated estrogens, A) Tablets
0.625 mg, 0.9 mg

Duramed has carefully researched both products for their dissolution profiles, measuring the rate of release of both sodium estrone sulfate and sodium equilin sulfate. The methods used to compare Cenestin™ and Premarin® were industry standards, as follows:

Method I — USP Apparatus 1 (basket) at 50 rpm in 900 mL purified water;
Method II — USP Apparatus 2 (paddle) at 50 rpm in 900 mL purified water.

Cenestin™ is a product of modern technology, incorporating a patented film-coating with a gum core matrix that consistently and slowly releases its conjugated estrogens over time. Cenestin™ shows very low variance in its dissolution curves. The acid-resistant film-coating slows dissolution in the stomach. Next, the gum core matrix first swells and then exposes the estrogens for slow absorption from the intestine into the bloodstream. This modern formula provides dependable relief from vasomotor symptoms.

Premarin® is a shellac-coated tablet, an older technology. Extensive industry testing over the last five decades has demonstrated that shellac-coating can break down with age, possibly affecting the *in vitro* release.

When you examine Figures 9 and 10, the result is clear: the *in vitro* variation in release of estrogens is much greater in Premarin® than in Cenestin™.[10]

FIGURE 9

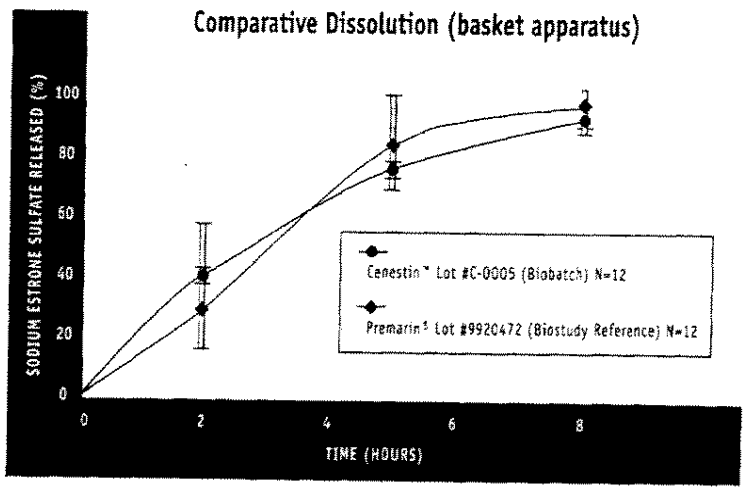
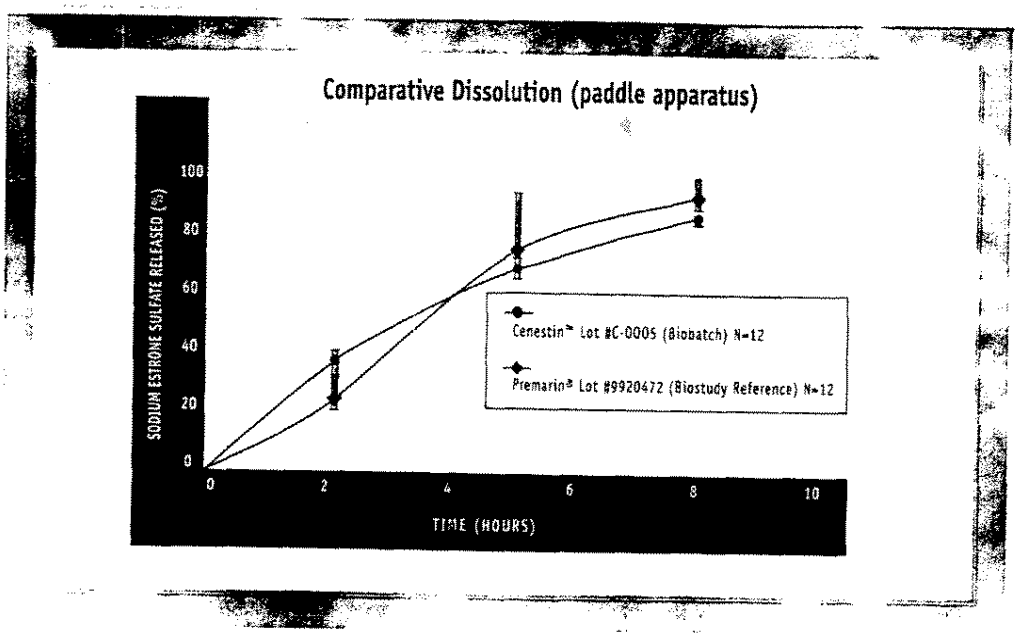


FIGURE 10



Bioequivalency

Cenestin™ and Premarin® are bioequivalent for the 2 major estrogens, estrone and equilin, based on an open-label, randomized, 2-treatment, 4-period, single dose, fully replicated, crossover study in 36 healthy, post-menopausal women, measuring bioequivalence for only these 2 major estrogens.[11]

TABLE 9
Summary Statistics of Relative Bioequivalence of Cenestin™ to Premarin® under Fasting Conditions

Drug Analyte	Pharmacokinetic Parameters		
	$AUC_{(0-72)}$	$AUC_{(0-a)}$	C_{max}
Total Estrone (baseline adjusted)	99.5%	99.7%	96.0%
Total Equilin	93.0%	93.0%	88.0%
Free Estrone (baseline adjusted)	109.4%	NM*	104.9%
Free Equilin	99.3%	NM*	95.9%

* NM — Not Meaningful

The results of this study, presented in Table 9, demonstrate that, under fasting conditions, the bioavailability of Cenestin™ and Premarin® is equal with regard to the two major estrogenic compounds, estrone and equilin.

The confidence intervals for all relevant pharmacokinetic parameters (AUC and C_{max} log-transformed) for all four analytes were within the range of 80% to 125% of the geometric mean of the reference product. Cenestin™, therefore, is bioequivalent to Premarin® with respect to estrone and equilin under fasting conditions in accordance with the currently accepted scientific criteria.

Figures 11 and 12 indicate the comparative total estrone and total equilin in plasma and the free estrone and free equilin in plasma, respectively.

FIGURE 11

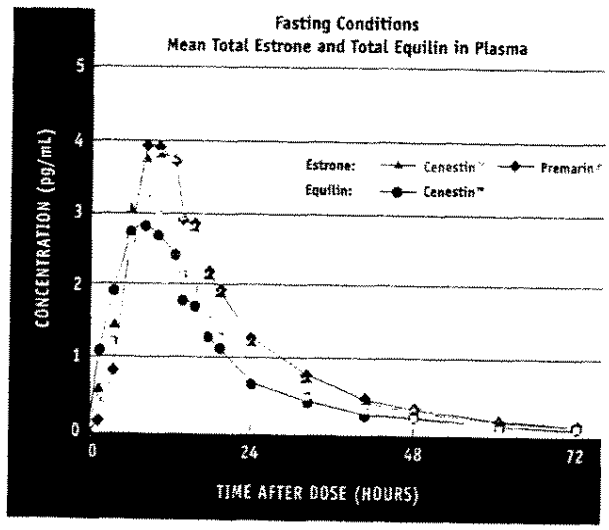
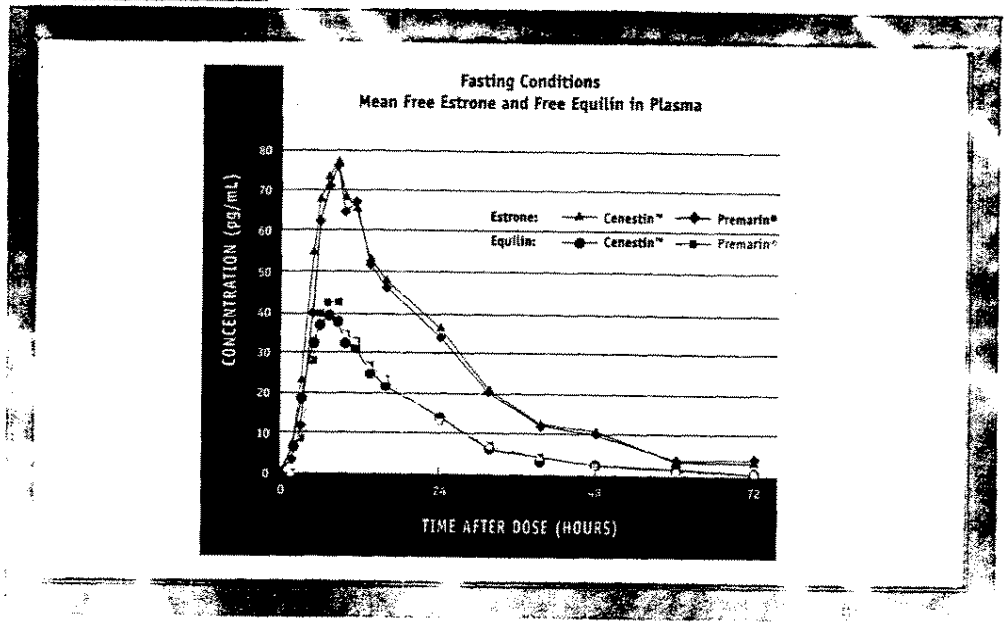


FIGURE 12



Content Uniformity

The stability of Cenestin™ in maintaining content uniformity is similar to that of Premarin®, as shown in a two-point time analysis of sodium estrone sulfate and sodium equilin sulfate components (Table 10).

TABLE 10
Content Uniformity of 0.625 mg Cenestin™ vs Premarin® for Two (2) Major Estrogen Components

Product	Sodium Estrone Sulfate		Sodium Equilin Sulfate		% of Label	
(Date determined)	Mean (mg)	RSD (%)	Mean (mg)	RSD (%)	Mean (%)	RSD (%)
Cenestin™ (6/93)	0.367	1.4	0.163	2.1	84.7	1.7
Cenestin™ (10/93)	0.368	1.4	0.164	1.4	85.0	1.4
Premarin® (3/93)	0.367	2.0	0.167	2.6	85.4	2.1
Premarin® (10/93)	0.368	1.4	0.164	1.4	85.2	2.0

Summary and Conclusions

For more than 50 years, there has not been a defined conjugated estrogens mixture alternative to Premarin®, the conjugated equine estrogens product derived from pregnant mares' urine, for the treatment of vasomotor symptoms of menopause. With the approval of Cenestin™, healthcare providers and their patients can now choose a synthetic conjugated estrogens replacement product derived exclusively from plant sources. Although there are other plant-derived estrogen products available, none offer the combination of conjugated estrogens and the slow release found in Cenestin™. When women have this additional choice in conjugated estrogens therapy, they may be more willing to begin such treatment and may be more likely to continue treatment once they have begun.

As the North American Menopause Society recommends, women should be involved in the decision to begin ERT or HRT, and physicians should encourage patients to discuss their preferences regarding estrogen therapy.[12] For many women, this plant-based conjugated estrogens product may be more appealing than one derived from the urine of pregnant horses.

Cenestin™ has been proven safe and effective for the treatment of vasomotor symptoms of menopause in a clinical trial of 120 women. This study was specifically designed to reflect the patient population seen in clinical practice. As such, the inclusion and exclusion criteria were more open than those of many other trials of estrogen class products. In this study, women taking Cenestin™ reported an 81% decrease in the number of moderate-to-severe hot flashes after 12 weeks of treatment. No serious adverse events occurred with Cenestin™; the most common complaints were headache, insomnia, asthenia, and paresthesia.

Cenestin™ is manufactured in a state-of-the-art facility and undergoes rigorous quality control checks to ensure a uniform and dependable product from batch to batch.

Cenestin™ is bioequivalent to Premarin® for the two major estrogenic components, estrone and equilin. The content uniformity and stability of Cenestin™ have been shown to be similar to Premarin®. Extensive dissolution testing demonstrates Cenestin™'s lower *in vitro* variability in rate of release of estrone and equilin over time.

With the aging of the population in the United States, the number of women seeking relief from the vasomotor symptoms of menopause (particularly hot flashes and night sweats) is expected to rise. Cenestin™ offers these women a safe and effective plant-based alternative to animal-based conjugated estrogens therapy.

Cenestin
(synthetic conjugated estrogens, B) tablets
0.625 mg, 0.9 mg

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6. Data on file, Duramed Pharmaceuticals, Inc.

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8. Premarin® is a registered trademark of Wyeth-Ayerst Laboratories, Inc., Philadelphia, PA.

9. Correspondence to Center for Drug Evaluation and Research, Docket No. 94P-0429/CP, Documents #34 to 39, May 5, 1997 (submitted), Food and Drug Administration, Rockville, MD.

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DURA med

PRESCRIBING INFORMATION

PATIENT PACKAGE INSERT

34

Cenestin™
(synthetic conjugated estrogens, A) Tablets

℞ only

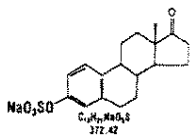
PRESCRIBING INFORMATION

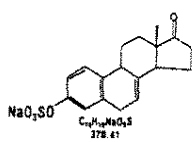
ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CARCINOMA. Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that natural estrogens are more or less hazardous than synthetic estrogens at equivalent estrogen doses.

DESCRIPTION

Synthetic conjugated estrogens, A tablets contain a blend of nine (9) synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17β-estradiol sulfate.

The structural formulae for these estrogens are:


Sodium Estrone Sulfate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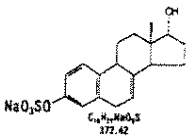
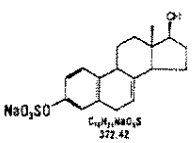
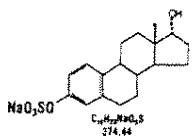
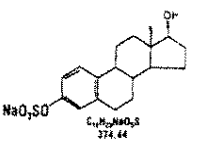

Sodium 17α-Dihydroequilin Sulfate


Sodium 17β-Dihydroequilin Sulfate


Sodium 17α-Estradiol Sulfate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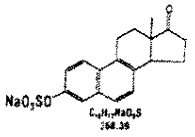
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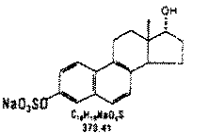
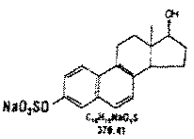

Sodium 17α-Dihydroequilenin Sulfate


Sodium 17β-Dihydroequilenin Sulfate

Tablets for oral administration, are available in 0.625 mg and 0.9 mg strengths of synthetic conjugated estrogens. Tablets also contain the following inactive ingredients: ethylcellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide, and triethyl citrate.

-0.625 mg tablets also contain: FD&C Red No. 40 aluminum lake.
-0.9 mg tablets do not contain any color additives.

CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

Absorption

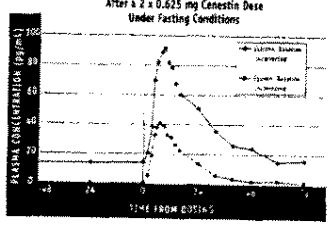
Synthetic conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. The Cenestin tablet releases the synthetic conjugated estrogens, A slowly over a period of several hours. Maximum plasma concentrations of conjugated and unconjugated estrogens are attained within 4 to 16 hours after oral administration.

Table 1
PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS IN HEALTHY POSTMENOPAUSAL WOMEN UNDER FASTING CONDITIONS

Pharmacokinetic Parameters of Unconjugated Estrogens Following a Dose of 2 x 0.625 mg Cenestin			
Drug	C_{max} (pg/mL) CV%	t_{max} (h) CV%	$AUC_{0\text{-}72h}$ (pg-hr/mL) CV%
Baseline-corrected estrone	84.5 (41.7)	8.25 (35.6)	1749 (43.8)
Equilin	45.6 (47.3)	7.78 (28.8)	723 (67.9)

Pharmacokinetic Parameters of Conjugated Estrogens Following a Dose of 2 x 0.625 mg Cenestin				
Drug	C_{max} (pg/mL) CV%	t_{max} (h) CV%	$t_{1/2}$ (h) CV%	$AUC_{0\text{-}72h}$ (pg-hr/mL) CV%
Baseline-corrected estrone	4.43 (40.4)	7.7 (30.3)	10.6 (25.4)	68.89 (39.2)
Equilin	3.27 (42.5)	5.8 (31.1)	9.7 (23.0)	46.46 (47.5)

Mean Plasma Concentration of Unconjugated Estrogens After a 2 x 0.625 mg Cenestin Dose Under Fasting Conditions



Food-Drug Interactions

The effect of food on the 0.625 and 0.9 mg tablets has not been studied.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone binding globulin (SHBG), and to a lesser degree to albumin. Conjugated estrogens bind mainly to albumin while the unconjugated estrogens bind to both albumin and sex-hormone binding globulin (SHBG).

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The apparent terminal elimination half-life ($t_{1/2}$) of conjugated estrone ranges from 4 to 18.5 hours and conjugated equilin from 4 to 17 hours.

Drug-Drug Interactions

There are no known drug interactions with estrogens.

Clinical Studies

A randomized, placebo-controlled multicenter clinical study was conducted evaluating the effectiveness of Cenestin for the treatment of vasomotor symptoms in 120 menopausal women. Patients were randomized to receive either placebo or 0.625 mg Cenestin daily for 12 weeks. Dose titration was allowed after one week of treatment. The starting dose was either doubled (2 x 0.625 mg Cenestin or placebo taken daily) or reduced (0.3 mg Cenestin or placebo taken daily), if necessary. Efficacy was assessed at 4, 8 and 12 weeks of treatment. By Week 12, 10% of the study participants remained on a single 0.625 mg Cenestin tablet daily while 77% required two (0.625 mg) tablets daily. The results in Table 2 indicate that compared to placebo, Cenestin produced a reduction in moderate-to-severe vasomotor symptoms at all time points (4, 8, and 12 weeks).

Table 2
Clinical Response*

Mean Change in Reduction in Vasomotor Symptoms			
	Cenestin (n=70)	Placebo (n=47)	Difference
Baseline Mean # (SD)	96.8 (42.6)	94.1 (33.9)	-
Week 4 Mean # (SD) Mean Change	28.7 (28.8) -68.1 (43.9)	45.7 (36.8) -48.4 (46.2)	- -19.9
Week 8 Mean # (SD) Mean Change	18.6 (25.0) -78.3 (49.0)	39.8 (39.1) -54.3 (49.2)	- -24.6
Week 12 Mean # (SD) Mean Change	16.5 (25.7) -80.3 (50.3)	37.8 (38.7) -56.3 (48.0)	- -24.7

Mean = Arithmetic Mean, SD = Standard Deviation
Difference = Difference between treatment LSMeans (Cenestin - Placebo)
**Intent-to-treat population = 117*

INDICATIONS AND USAGE

Cenestin (synthetic conjugated estrogens, A) Tablets are indicated in the treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see PRECAUTIONS).
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast (except in appropriately selected patients being treated for metastatic disease).
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS

1. **Induction of malignant neoplasms.**
   a. **Endometrial cancer.** The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.
   b. **Breast cancer.** While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, there are conflicting data whether there is an increased risk in women using estrogens for prolonged periods of time, especially in excess of 10 years.

DURAmed

2. **Venous thromboembolism.** Three epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The findings were similar for ERT alone or with added progestin and pertain to commonly used ERT types and doses, including 0.625 mg or more per day orally of conjugated estrogens, 1 mg or more per day orally of estradiol, and 50 µg or more per day of transdermal estradiol. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year.
3. **Cardiovascular disease.** Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.
4. **Hypercalcemia.** Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.
5. **Gallbladder disease.** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

PRECAUTIONS

A. General

1. **Addition of a progestin when a woman has not had a hysterectomy**
   Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone.
   There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. These include:
   (a) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL);
   (b) impairment of glucose tolerance; and
   (c) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point.
   The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.
2. **Elevated blood pressure**
   Substantial increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens in a small number of case reports. A generalized effect of estrogen therapy on blood pressure was not found in the one randomized, placebo-controlled study that has been reported.
3. **Familial hyperlipoproteinemia**
   Estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.
4. **Impaired liver function**
   Estrogens may be poorly metabolized in patients with impaired liver function.

B. Information for the Patient
See text of PATIENT LABELING, below.

C. Laboratory Tests
Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.

D. Drug/Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.

E. Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. See CONTRAINDICATIONS and WARNINGS.

F. Pregnancy
Estrogens are not indicated for use during pregnancy or the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Treatment with diethylstilbestrol (DES) during pregnancy has been associated with an increased risk of congenital defects and cancer in the reproductive organs of the fetus, and possibly other birth defects. The use of DES during pregnancy has also been associated with a subsequent increased risk of breast cancer in the mothers.

G. Nursing Mothers
As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of postpartum breast engorgement.

H. Pediatric Use
Safety and efficacy of Cenestin for the treatment of vasomotor symptoms due to hypoestrogenism in pediatric patients have not been established.

ADVERSE REACTIONS

See **WARNINGS** and **PRECAUTIONS** regarding the potential adverse effects on the fetus, the induction of malignant neoplasms, gallbladder disease, cardiovascular disease, elevated blood pressure and hypercalcemia. In a 12-week clinical trial that included 72 women treated with Cenestin and 48 women treated with placebo, the following adverse events occurred at a rate ≥ 5% (see **Table 3**).

Table 3
Number (%) of Patients with Adverse Events With a Greater than 5% Occurrence Rate By Body System and Treatment Group

Body System Adverse Event	Cenestin n (%)	Placebo n (%)	Total n (%)
Number of Patients Who Received Medication	72 (100)	48 (100)	120 (100)
Number of Patients With Adverse Events	68 (94)	43 (90)	111 (93)
Number of Patients Without Any Adverse Events	4 (6)	5 (10)	9 (8)
Body As A Whole			
Abdominal Pain	20 (28)	11 (23)	31 (26)
Asthenia	24 (33)	20 (42)	44 (37)
Back Pain	10 (14)	6 (13)	16 (13)
Fever	1 (1)	3 (6)	4 (3)
Headache	49 (68)	32 (67)	81 (68)
Infection	10 (14)	5 (10)	15 (13)
Pain	8 (11)	9 (19)	17 (14)
Cardiovascular System			
Palpitation	15 (21)	13 (27)	28 (23)
Digestive System			
Constipation	4 (6)	2 (4)	6 (5)
Diarrhea	4 (6)	0 (0)	4 (3)
Dyspepsia	7 (10)	3 (6)	10 (8)
Flatulence	21 (29)	14 (29)	35 (29)
Nausea	13 (18)	9 (19)	22 (18)
Vomiting	5 (7)	1 (2)	6 (5)
Metabolic and Nutritional			
Peripheral Edema	7 (10)	6 (13)	13 (11)
Musculoskeletal System			
Arthralgia	18 (25)	13 (27)	31 (26)
Myalgia	20 (28)	15 (31)	35 (29)
Nervous System			
Depression	20 (28)	18 (38)	38 (32)
Dizziness	8 (11)	5 (10)	13 (11)

(Table 3 continued)

Body System Adverse Event	Cenestin n (%)	Placebo n (%)	Total n (%)
Hypertonia	4 (6)	0 (0)	4 (3)
Insomnia	30 (42)	23 (48)	53 (44)
Leg Cramps	7 (10)	3 (6)	10 (8)
Nervousness	20 (28)	20 (42)	40 (33)
Paresthesia	24 (33)	15 (31)	39 (33)
Vertigo	12 (17)	12 (25)	24 (20)
Respiratory System			
Cough Increased	4 (6)	1 (2)	5 (4)
Pharyngitis	6 (8)	4 (8)	10 (8)
Rhinitis	6 (8)	7(15)	13 (11)
Urogenital System			
Breast Pain	21 (29)	7 (15)	28 (23)
Dysmenorrhea	4 (6)	3 (6)	7 (6)
Metrorrhagia	10 (14)	3 (6)	13 (11)

The following additional adverse reactions have been reported with estrogen therapy:

1. *Genitourinary system.* Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.
2. *Breasts.* Tenderness, enlargement.
3. *Gastrointestinal.* Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; gallbladder disease.
4. *Skin.* Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.
5. *Eyes.* Steepening of corneal curvature; intolerance to contact lenses.
6. *Central Nervous System.* Headache, migraine, dizziness; mental depression; chorea.
7. *Miscellaneous.* Increase or decrease in weight; reduced carbohydrate tolerance; aggravation or porphyria; edema; changes in libido.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

For treatment of moderate-to-severe vasomotor symptoms associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen. Initial doses of 0.625 mg are recommended with titration up to 1.25 mg. Medication should be discontinued as promptly as possible. Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

HOW SUPPLIED

Cenestin (synthetic conjugated estrogens, A) Tablets,
- 0.625 mg tablets are available in containers of 30 (NDC 51285-442-30), 100 (NDC 51285-442-02), and 1000 (NDC 51285-442-05).
  Tablets are round, red colored, film-coated, and are debossed with letters, db, and number, 42.
- 0.9 mg tablets are available in containers of 30 (NDC 51285-443-30), 100 (NDC 51285-443-02), and 1000 (NDC 51285-443-05).
  Tablets are round, white, film-coated, and are debossed with letters, db, and number, 43.

Store at 25°C (77°F); excursions are permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]
Dispense in tight container as defined in USP.
Dispense in child-resistant packaging.
Dispenser: Include one "Information for the patient" leaflet with each package dispensed.

Manufactured by: Duramed Pharmaceuticals, Inc.
Cincinnati, OH 45213 USA

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Cincinnati, Ohio 45213 U.S.A.

Made from plants! Isn't that cool?™

Cenestin
(synthetic conjugated estrogens, A) Tablets
0.625 mg, 0.9 mg

VIK 000941

Cenestin™
(synthetic conjugated estrogens, A) Tablets

PATIENT PACKAGE INSERT

INTRODUCTION

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks are acceptable in comparison to the benefits. If you use estrogens, check with your doctor to be sure you are using the lowest possible dose that works, and that you don't use them longer than necessary. How long you need to use estrogens will depend on the reasons for use.

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS

If you use any drug that contains estrogen, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

USES OF CENESTIN

To reduce moderate or severe menopausal symptoms.

Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden drop in estrogen levels causes "surgical menopause".

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.

WHO SHOULD NOT USE CENESTIN

Cenestin should not be used:

- **During pregnancy.**
  If you think you may be pregnant, do not use any form of estrogen-containing drug. Using some types of estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.
- **If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warning).**
  Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment.
- **If you have had cancer.**
  Since estrogens may increase the risk of certain types of breast and uterine cancer, you should not use estrogens unless your doctor recommends that you take it. (For certain patients with breast or prostate cancer, estrogens may help.)
- **If you have any circulation problems.**
  Men and women with abnormal blood clotting conditions should avoid estrogen use (see DANGERS OF ESTROGENS, below).
- **After childbirth or when breastfeeding a baby.**
  Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see DANGERS OF ESTROGENS, below).

DANGERS OF ESTROGENS

- **Cancer of the uterus.**
  Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. Because of this risk, it is important to take the lowest dose that works and to take it only as long as you need it.
  Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (see also OTHER INFORMATION, below).
  If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.
- **Cancer of the breast.**
  Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.
  Regular breast examinations by a health professional and monthly self-examination are recommended for all women. Yearly mammography is recommended for women beginning at age 50.
- **Abnormal blood clotting.**
  Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs causing serious problems. These problems may include stroke (by cutting off blood to the brain), heart attack (by cutting off blood to the heart), a pulmonary clot (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability.
- **Gallbladder disease.**
  Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

Nausea and vomiting.
Breast tenderness or enlargement.
Enlargement of benign tumors of the uterus (fibroids).
Retention of excess fluid.
Spotty darkening of the skin, particularly on the face.

USE IN CHILDREN

Cenestin has not been shown either effective or safe for use by infants, children, or adolescent boys or girls.

REDUCING THE RISKS OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

- **See your doctor regularly.**
  While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation.
- **Reassess your need for estrogens.**
  You and your doctor should reevaluate whether or not you still need estrogens every three to six months.
- **Be alert for signs of trouble.**
  If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:
  Abnormal bleeding from the vagina (possible uterine cancer)
  Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)
  Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)
  Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)
  Yellowing of the skin or eyes (possible liver problems)
  Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.

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